

**Ketamine/Propofol Admixture “Ketofol” at Induction in the Critically III Against
Etomidate: KEEP PACE Trial**

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Etomidate: KEEP PACE Trial**

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ABSTRACT

Endotracheal intubation is a procedure that may cause significant hemodynamic perturbations and can severely impact the outcome of the critically ill. To ensure a safe outcome during this particular procedure, there are many factors that the clinician is faced with. One decision that confronts the critical care physician involves the correct combination of medications with which to facilitate such a safe outcome. Given the reported hemodynamic stability, etomidate is a medication that is chosen by many providers in this particular situation. However, its association with a possible increase in mortality makes it less than ideal for a number of critical care physicians. In recent years, an admixture of propofol and ketamine has been studied that demonstrates hemodynamic stability based on the balancing of the hemodynamic effects of these two individual agents alone. This novel medication combination, sometimes referred to as “ketofol”, may offer a valuable alternative to the critical care physician. Therefore, a randomized parallel-group clinical trial of adult critically ill patients admitted to St. Marys medical ICU (MB-6B/G) or surgical ICU (MB-7D/E) or Methodist medical/surgical ICU (10-3/10-4) at Mayo Clinic Rochester who meet the criteria designated below for which urgent and/or emergent intubation is needed will receive one of two interventions based on stratified randomization. The “active” intervention arm will receive ketamine/propofol (ketofol) to facilitate endotracheal intubation. The comparison arm will receive etomidate. The primary outcome will focus on hemodynamic data recorded during the first 15 minutes post-administration with secondary outcomes addressing intensive care unit length of stay, 28 day in-hospital mortality, and vasoactive medication use, among others.

Specific Aims

Critically ill patients often require urgent and/or emergent intubations for diagnostic and/or therapeutic interventions. Preparation and administration of sedation for intubations are of vital importance, especially in this patient population where many patients have multiple co-morbidities. Etomidate is a medication that was developed to afford hemodynamic stability during this process. With the recent drug shortages across the country, alternatives to this medication are necessary and drug combinations may provide an alternative route.¹⁻² Furthermore, etomidate's association with adrenal suppression and possibly increased mortality among critically ill patients makes it less than ideal for a number of critical care physicians.³⁻⁹ According to a systematic review in 2011, etomidate anesthesia in the intensive care unit resulted in an increased relative risk for both adrenal insufficiency (1.64) and mortality (1.19).⁵ A second study reported in 2012 on over 700 patients demonstrated an increase in relative risk of death (1.20) for patients who received etomidate as compared to an alternative agent.³ There are other medications that are available but each with its own set of concerns and none are reported to offer stable hemodynamics during this process such as etomidate.¹⁰⁻¹¹ In recent years, an admixture of propofol and ketamine has been studied that demonstrates hemodynamic stability based on the balancing of the hemodynamic effects of these two individual agents alone.^{10,12-13} Most of these studies have taken place in the emergency department with focus on continuous infusions and compared with multiple medications.¹⁴⁻¹⁸ The literature is absent with regards to a comparison of this combination against one that is purported to afford hemodynamic stability such as etomidate.^{10,19}

The **overall goal** of this research proposal is to assess the hemodynamics of a particular drug combination (ketamine/propofol) that may be used in critically ill patients in urgent and/or emergent need of endotracheal intubation with reduced effects on mortality as compared to etomidate. **The objective** is to obtain preliminary data on the hemodynamics of this combination within the critically ill population. **The central hypothesis** is that this combination will produce smaller decreases in mean arterial pressure as compared to etomidate within the first 15 minutes post-administration. We are well prepared to undertake the proposed research as we have an investigative team with experience in this drug combination.

Primary Specific Aim: To determine if the decrease in mean arterial pressure for the ketamine/propofol group at a 1:1 dose ratio is lower as compared to the etomidate group within the first 15 minutes post-administration in patients in need of urgent and/or emergent endotracheal intubation, as defined by any intubation within the intensive care unit excluding intubations for elective procedural events and codes.

Hypothesis: The decrease in mean arterial pressure for the ketamine/propofol arm will be reduced as compared to the etomidate arm during the first 15 minutes post-administration within the population of critically ill patients needing urgent and/or emergent endotracheal intubation.

Secondary Specific Aim 1: To determine whether this admixture is associated with decreased in-hospital/28-day mortality as compared to etomidate in the critically ill.

Hypothesis 1: The in-hospital/28 day mortality among patients in the ketamine/propofol combination will be decreased as compared to the in hospital/28-day mortality in the etomidate arm.

Secondary Specific Aim 2: To determine if this admixture is associated with decreased use of vasoactive medication administration (e.g., dopamine, phenylephrine, norepinephrine, epinephrine or vasopressin) from time 0 to 24 hours post-administration as compared to etomidate in the critically ill.

Hypothesis 2: The use of vasoactive medications to restore the blood pressure post-administration will be reduced in the ketamine/propofol combination as compared to the etomidate group.

To evaluate the above specific aims, we will randomize 160 critically ill patients in need of urgent and/or emergent intubation to one of two arms through a comparison trial. This study will provide insight into a novel drug combination that may be used by some health care professionals when facing drug shortages and in need of an equivalent alternative for the hemodynamically unstable patient without the cost of increased mortality.

RESEARCH STRATEGY

A. Significance

A.1. Ketamine and Propofol

Propofol is a non-opioid, non-barbiturate, sedative-hypnotic agent with rapid onset and short duration of action. It reliably produces sedation, amnesia, and general anesthesia but because of the associated hemodynamic instability when used alone, its use in the critical care setting is limited. Ketamine is a phencyclidine derivative with fairly rapid onset and short duration of action. It causes little or no respiratory and cardiovascular depression and has analgesic properties. It may, however, cause hemodynamic instability and alterations if given alone with propensity of effects that are opposite that of propofol, especially relevant in the cardiac and neurological population.^{11,20}

A.2. Drug Shortages

In recent years, there has been interest in finding alternative medications with which to sedate patients for particular procedures. This has risen in part by the continued drug shortages experienced throughout the country.¹⁻² Due to these drug shortages, various medications have been combined in order to reduce waste and conserve already depleted drug shortages in the healthcare setting. However, combining medications can be hazardous with issues relating to compatibility and potentiation of individual side effects of the parent drugs.

A.3. Ketamine/Propofol Admixture Compatibility

One such combination that has gained much interest as of late due to the balancing of the individual effects of either drug alone involves the combination of ketamine and propofol. This medication combination has been demonstrated to be safe in specific dose combinations.^{10,12} Furthermore, this particular combination has been tested to assess whether there are any precipitation of components or ill effects from combining these two medications. These studies have shown stability of ketamine in the presence of propofol.²¹⁻²²

A.4. Ketamine/Propofol Admixture

Much of the work regarding these two agents derives from studies focusing on procedural sedation in the emergency department as a continuous infusion.¹²⁻¹⁵ These studies have identified the benefits of both medications while diminishing the side effects from both parent compounds when in combination. A few studies have shown stability of systemic hemodynamics.^{10,12,15-16} Moreover, a recent study demonstrated evidence of ketofol's stability on cerebral hemodynamics as well as on systemic hemodynamic measurements.²³ While some studies have demonstrated direct comparisons of ketofol to other agents during induction, this has been limited.^{10,19} Therefore, relatively little data arrive at outcomes targeting hemodynamics and there are no studies to the authors' knowledge regarding this admixture with comparison to etomidate regarding hemodynamics, or mortality.¹⁰ This is likely due to no standardized admixture of ketofol. A study in 1995 did address a dose response relationship with this combination on healthy volunteers with no comparison against another agent. However, this was a homogenous group of patients that involved Asian women.²⁴

A.6. Rational for Approach

If the proposed aims are achieved, this research will provide clinicians with evidence for an alternative medication to use when faced with the unstable critically ill patient in need of urgent and/or emergent intubations. Through accomplishment of the aims, clinicians will not feel necessary to use etomidate in the critically ill patient who may become unstable. According to studies previously mentioned, this may result in improved mortality for critically ill patients. Moreover, this combination would, in theory, provide pain control and potentially reduce the amount of sedatives necessary to keep the patient safe during their intensive care unit stay. With the possible reduction in sedative/analgesic medications, this may translate into improved patient related outcomes and total reduced cost for the institution. A follow-up analysis will need

to be performed to assess possible institution cost savings. This study will provide valuable insight into dose response relationships involving this particular medication and will be among the first to compare against an agent such as etomidate in the critical care environment. Lastly, this admixture will provide an alternative to hospitals who are in midst of drug shortages. Through the use of this medication combination, supplies may be better preserved than with each medication used separately in larger doses.

B. INNOVATION

The proposed research adds considerably to the field of critical care medicine. The use of a ketamine/propofol admixture as an alternative anesthetic induction agent to provide care to the critically ill unstable patient in need of urgent and/or emergent endotracheal intubation is a novel concept. The use of such a drug combination has not been rigorously tested in this particular setting. Data are available on specific dose ratios of this admixture against various alternative agents.^{13,17,19} However, there is no data to the authors' knowledge that compares this drug combination against etomidate.

The weight-based dosing used in this study and in this particular setting has not been used in previous studies. A study comparing various dose ratios based on body weight of this admixture was performed in Asian women in the mid 90's. However, this study did not use the prescribed weight based doses as in this study.²⁴ Therefore, the prescribed doses as used in this study protocol along with its use in the critical care environment is novel.

This drug combination is appealing for many reasons. One important reason relates to the question of an ideal anesthetic agent. An ideal anesthetic agent would include properties of sedation, amnesia and analgesia without cardio-respiratory effects.²⁰ Of the approved listed medications for induction of anesthesia, ketamine is the only agent reported to provide significant pain relief.^{11,20} The combination of ketamine with propofol yields an admixture that is very close to an ideal anesthetic agent without further ill effects on the patient as compared to other agents with which to sedate patients during endotracheal intubation. Therefore, although this drug combination has been used for many years, it has only recently been realized that the potential benefits of this combination may have a strong positive impact on patient outcomes in any given setting.

C. APPROACH

C.1. Preliminary Studies

The principal investigator recently completed a comparison of a 1:2 ketamine/propofol combination against propofol only at induction in American Society of Anesthesiologists 1-2 patients and demonstrated improved hemodynamic indices with ketofol as compared to propofol only. In this paper, the authors' noted that a fixed dose admixture of ketamine and propofol against etomidate in the critically ill is warranted.¹⁰ Therefore, this is a follow-up study to the above mentioned reference.

Limitations of Study: The study had several significant limitations. First, our study was in healthy patients and therefore not clinically relevant. Second, the comparison agent was one that is known to cause hemodynamic instability at induction and therefore, the results could have been anticipated. Finally, our primary outcome was a reduction in systolic blood pressure specified by a certain percentage and not on absolute mean arterial pressure.

C.2. Definitions

1) Ketofol: ketamine and propofol in combination with specified dose ratio; 2) Urgent and/or emergent intubation: Any intubation in the intensive care unit excluding elective procedural intubations; 3) True emergent situation: any situation that is defined as a code. 4) 28 day in-hospital mortality: Mortality that occurs before hospital discharge or hospital day 28, whichever

comes first. 5) Post-menopausal: 12 consecutive months or more since last reported period or documented post-menopausal status in EMR.

C.3. Current Proposal Overview

Stratified Randomized parallel-group clinical trial of adult critically ill patients admitted to St. Marys medical ICU (MB-6B/G) or surgical ICU (MB-7D/E), or Methodist medical/surgical ICU (10-3/10-4) at Mayo Clinic Rochester who meet the criteria designated below for which urgent and/or emergent intubation was needed and who received one of two interventions based on stratified randomization. The “active” intervention arm will receive ketamine/propofol (ketofol) to facilitate endotracheal intubation. The comparison arm will receive etomidate. Given that critically ill patients may require reduced doses of medications compared to patients presenting electively to surgery, induction doses in both groups will be reduced.²⁸ The two groups will receive two doses with the reduced dosing stated above and will use the first dose at induction. The second dose will be available as a rescue should the provider need further sedation. The decision for the rescue dose will be made by the provider at the time of induction for intubation based on the clinical status of the patient. Demographic and outcome variables will be collected prospectively and analyzed after all patients have completed the study procedures.

C.4. Participants

Subjects will be eligible to participate if they: 1) are at least 18 years of age; 2) are surgical and medical intensive care unit patients requiring endotracheal intubation and treating consultant agrees to study plan and will follow drug randomization. Individuals will be excluded from study participation if they: 1) have intracranial pathology such as acute head bleed or intracranial mass of significant size causing elevated ICP or acquired head injury documented during current hospitalization; 2) have chronic opiate-dependence as defined by those patients on methadone, buprenorphine, buprenorphine-naloxone or naltrexone as an outpatient; 3) have a severe psychiatric illness defined as currently being treated for bipolar and/or schizophrenia disorder; 4) have egg allergies; 5) have any contraindications to fentanyl, midazolam, ketamine, propofol or etomidate; 6) have an intubation performed during true emergent situations such as codes where standard practice is not to use induction drugs; 7) do not have a documented weight and/or are greater than 140kg or less than 30kg; 8) have had prior participation in the current study; 9) are on continuous infusions of propofol, midazolam, lorazepam, fentanyl or dexmedetomidine in the previous 24 hours; 10) undergo a procedural intubation; 11) are of child-bearing age, defined as 18-50 years, and do not have a documented pregnancy test at our institution confirming that they are not pregnant or who do not have a confirmed surgical procedure or medical history preventing pregnancy, (i.e., tubal ligation, hysterectomy, post-menopausal). The timing of the pregnancy test at which the investigative team will consider a subject to be non-pregnant is a documented negative test during current hospitalization or upon direct transfer from outside institution during current illness. If the investigative team does not know at the time of emergency intubation that a female of 18-50 years has a documented negative pregnancy test, AND they do not have a confirmed surgical procedure or medical history preventing pregnancy, she will not be allowed to participate in the clinical trial. No time will be spent looking for this information in fear of delaying a needed intervention and therefore, the female will be excluded.

C.5. Rational for Inclusion/Exclusions

After a thorough review of the literature, we have identified specific conditions in which it is recommended to avoid the use of the medications under study in certain situations such as acute head injury or severe psychiatric illness.

C.6. Randomization

A computerized randomization schedule will be generated by a statistician not involved in determination of patient eligibility, drug administration, or outcome assessment. Randomization will be performed using 2 stratification factors (unit: 6B/G, 7D/E, 10-3/4; shock state: Mean Arterial Pressure (MAP) ≥ 65 or MAP < 65). Within each strata, the randomization will be performed using blocks of size $N=4$ to ensure that after every 4th patient is randomized within a given strata there are an equal number of patients assigned to each treatment group. Randomization will be accomplished by using opaque envelopes. The randomization envelopes will contain a card with the study drug imprinted onto it to which the patient was randomized. In addition, the envelopes will contain a role checklist for the care team, a study subject identification number, and a dosing chart for correct drug administration. The bedside nurse along with the core study staff will obtain the correct randomization envelope based on the patient's current MAP vital sign. The core study staff will evaluate for exclusions prior to opening the envelope. Additionally, the role checklist and dosing chart will be provided to the respective units.

C.7. Medication Preparation

The medications will be provided through the drug dispensing machine on the respective units, the Pyxis machine. Propofol (one 20ml vial) and ketamine (one 20ml vial) are to be aseptically drawn from a standard concentration (10mg/ml) into a 60ml syringe by the assigned bedside nurse. Within the concealed randomization envelope, the nurse will find a dosing chart in milliliters to be administered to the patient based on the patient's weight in kilograms. The syringes used to deliver the study medications will contain the appropriate Investigational New Drug (IND) labeling and study subject identification. Etomidate (two 10ml vials) is to be aseptically drawn from a standard concentration (2mg/ml) into a 35ml syringe. The bedside nurse will find a similar dosing chart for etomidate. The 35ml syringe used to deliver the study medication will contain the appropriate IND labeling and study subject identification number. The etomidate dose will be weight based such that it represents 0.15mg/kg of etomidate. The initial 0.15mg/kg will be considered the induction dose and a second dose of 0.15mg/kg will serve as a rescue dose if deemed clinically necessary. Should the clinical care team need more than 0.3mg/kg of etomidate, they may use the remainder of the study syringe as dedicated by the critical care clinician. We do not anticipate this will happen often given the initial prescribed doses. However, they may not cross over to use ketamine or propofol after etomidate has been administered. The ketofol dose will also be weight based such that it represents 0.5mg/kg of ketamine and 0.5mg/kg of propofol. The initial 1mg/kg (0.5mg/kg of ketamine and propofol each) will be considered the induction dose and a second dose of 1mg/kg will serve as a rescue dose if deemed clinically necessary. Again, should the clinical care team need more than 1mg/kg of ketamine and propofol each, they may use the remainder of the study syringe as dedicated by the critical care clinician. Furthermore, the care team may use additional ketamine or propofol only at their discretion. We do not anticipate this will happen often given the initial prescribed doses. However, they may not cross over to use etomidate after ketofol has been administered. This dose is based on the dose response curves from Hui et.al.²⁴ In this study, a 0.5mg/kg dose of ketamine and propofol produced anesthesia in roughly 50% of healthy patients who did not receive other sedatives and were not critically ill. We know that the critically ill are provided with additional sedatives for various reasons and that certain medications (e.g., propofol) have increased potency in shock patients (see reference 28). If the rescue dose is given in this study, the patient will have received a standard induction dose of ketamine. This is a standard induction dose for an elective surgical patient and not a critically ill patient. Furthermore, the patient will also have been given propofol. The decision to use the rescue dose will be made by the provider at the time of induction for intubation. This decision will be dependent on the clinical status of the patient. There are three main conditions in which the critical care provider may need additional anesthetic agent during endotracheal intubation. These include but are not limited to: 1) patient movement/purposeful response to the intervention; 2) difficult intubation; 3) or inadvertent under-dosing. Therefore, the only decision made by the provider will center on whether they request the rescue dose and/or additional doses. The bedside nurse will be provided with a checklist of tasks to be performed during the urgent and/or emergent intubation. The checklist

will be contained within the concealed randomization envelope. The remaining study medications will be disposed through Pyxis per usual practice.

C.8. Study Protocol

Consent: Given the uncertainty of urgent and/or emergent intubations along with the time necessary for preparation of the study drugs and the ethical issue of consenting a potential unstable patient to a treatment, we will provide community consultation consisting of meetings with community members. Community consultation plans will involve 4-10 focus group sessions, advertisements on the Mayo Clinic external website and informational flyers distributed within the community. Through these plans, the community will be notified of the study and the understanding that all patients admitted to the above named critical care units at Saint Marys and Methodist Hospital who meet the inclusion/exclusion criteria will be included in this study (please refer to consent process development plan document). Study coordinators would then follow up with the patient and/or their legally authorized representative to indicate their involvement in the study. If time allows, consent will be obtained prospectively. However, this will likely not happen for the majority of patients given the issues outlined above. The investigative team will make every effort to prospectively contact the legally authorized representative prior to enrolling the patient in the current study. If the legally authorized representative or family member is available at the time the subject is clinically in need of a breathing tube, the study coordinators will attempt to contact these members while the bedside nurse is preparing the medications. The study coordinators will explain that a research study involving medications used and approved by the FDA for assistance with placement of a breathing tube is currently underway. They will explain that two individual medications already in use for this purpose may have beneficial effects when combined together and that the investigative team is simply trying to collect data on this unique combination for which no approval has been granted by the FDA as of yet. The legally authorized representative will have the opportunity to provide consent or decline participation of the subject at this time. If they declined participation of subject, the study coordinators will notify the bedside nurse immediately and the study will cease. If the legally authorized representative is not available at the time of study enrollment, the team will attempt to contact additional family members to provide an opportunity to consent to the subject's participation. However, as stated previously, this will likely not be possible in truly urgent and/or emergent situations. If the subject has been enrolled in the current study without prior contact from the patient, legally authorized representative, or additional family members, the investigative team will notify the legally authorized representative regarding subject's enrollment and an opportunity to withdraw the subject from the study if they deem it necessary. Due to the nature of the present study and the environment that it will be conducted in, we believe that the only feasible route in performing a study such as this is under the emergent use research guidelines as previously published by the Food and Drug Administration (www.fda.gov/RegulatoryInformation/Guidances). Below are the conditions that satisfy emergent use research in the document and our responses to each.

1. The human subjects are in a life-threatening situation that necessitates urgent intervention:
 - a. Unlike intubations performed outside the intensive care unit, e.g. the operating room, placement of an endotracheal tube is done under urgent/emergent conditions and rarely electively. Those intubations that are performed in the intensive care unit under elective conditions, e.g. for bronchoscopy/endoscopy, will not be included in the current study. Elective intubations in the intensive care unit are done within the context of a stable patient and therefore any anesthetic induction agent may be used safely with no need for the above study drug. The true benefit of the study drug involves the critically ill patient who is hemodynamically unstable but is in need of an endotracheal tube.
2. Available treatments are unproven or unsatisfactory:

- a. There are several alternative anesthetic agents that are available that may be used to facilitate placement of an endotracheal tube. However, these alternatives are either unproven or unsatisfactory for the condition at hand.
 - 1) Etomidate has proven efficacy in providing stable hemodynamics. As referenced above, however, this comes with significant drawbacks with the most significant being known adrenal suppression and a potential increase in mortality.
 - 2) Propofol alone is unsatisfactory as the administration of this anesthetic agent may lead to dangerously low mean arterial pressures secondary to vasodilation and bradycardia, especially within the critically ill patient. This agent is acceptable for those patients who have placement of an endotracheal tube for elective purposes, as these patients are not hemodynamically unstable.
 - 3) Ketamine as a sole sedative has some concerns in the intensive care unit for routine use. One study directly comparing ketamine to etomidate in critically ill patients did show some benefits of ketamine. However, the ketamine administration was done in a non-critical care setting prior to ICU admission. In addition, this study did involve waiver of consent due to the emergent nature of the intervention and the non-feasible alternative of obtaining informed consent²⁷. Ketamine use as a sole agent also has some unsatisfactory cardiovascular adverse effects. Ketamine administration is commonly associated with elevations in blood pressure and heart rate. Arrhythmias may also occur. These cardiovascular effects of ketamine are dependent on concentration and secondary to central nervous system stimulation and inhibition of norepinephrine reuptake^{11,20,29-31}. These elevations in blood pressure and heart rate can have a detrimental effect on patients with underlying heart disease³². Additionally, ketamine possess properties that may make intubation attempts difficult due to the increased muscular tone at certain dosage levels²⁰. Evidence suggests that difficult intubations lead to increased mortality in critically ill patients from repeated airway manipulations³³⁻³⁴. Finally, an increased risk of emergence delirium with ketamine is clearly demonstrated in the product information and throughout the literature. Since the above adverse effects are dose related, a reduction in dose by using ketamine in a combination with propofol may improve these adverse outcomes. Therefore, the use of smaller rather than larger doses is likely to be of benefit as possibly evident in recent case reports of septic shock patients suffering cardiac arrest after receiving 2mg/kg of ketamine³⁵.
 - 4) Benzodiazepines are unsatisfactory as there is evidence demonstrating increased risk of both delirium and mortality with the use of benzodiazepines³⁶⁻³⁷.
 - 5) Barbiturates are unsatisfactory as these agents may also lead to unacceptable decreases in mean arterial pressure, secondary to a decreased systemic vascular resistance and decreased cardiac output.
 - 6) Thus, the combination of ketamine and propofol can offset the hemodynamic extremes of either drug with the combination resulting in potentially more stable hemodynamics and a safer alternative than either drug alone.
3. Rationale for therapeutic window:
 - a. The interval period under study was chosen due the alpha half-life or redistribution half-life from the central compartment of the three drugs. The redistribution half-life of all three drugs is approximately 2-16 minutes, thus the reason for time frame

chosen in the current study. The alpha half-life is clinically responsible for the anesthetic effect seen in medical practice²⁰.

4. Collection of valid scientific evidence is necessary to determine the safety and effectiveness of the intervention in this population:
 - a. Insufficient evidence exists regarding the safety and efficacy of this drug admixture within the critically ill. As referenced above, a large amount of the data regarding ketamine/propofol admixture involves patients in the operating room or the emergency department. Although this drug combination (ketofol) is currently being used clinically in several clinical care settings (emergency department, operating room, and ICU), data is not available regarding the use of this admixture in the critically ill population in an ICU setting.
5. Obtaining informed consent is not feasible because the subjects are not able to give their informed consent as a result of their medical condition:
 - a. Patients in the intensive care unit requiring placement of an endotracheal tube are not in a position to comprehend or sign a document pertaining to clinical research. These patients may be in respiratory failure and/or are unstable and to consent this patient population would be un-ethical. Several factors play into the cognitive disability of critically ill patients. For example, delirium is highly prevalent among critically ill patients ranging anywhere from 20% to as high as 80%³⁸. Several studies point to the inability of critically ill patients who are unable to consent. For example, a study involving over 400 patients in the intensive care unit utilizing pulmonary artery catheters demonstrated that only 2.6% of patients were able to consent to this intervention³⁹. In fact, some studies are not feasible without consent waiver due to the critical condition of the patient^{27,40}. Thus, the process of consenting this patient population is questionable.
6. The intervention must be administered before the consent can be obtained from the subject's legally authorized representative:
 - a. Emergent endotracheal intubations within the intensive care unit happen quickly and oftentimes, a legally appointed representative is not available for several reasons. In an observational trial for traumatic brain injury in 2007, investigators demonstrated that the number of patients with relatives available for research authorization was only 3% and 25% at 1 and 3 hours post-injury⁴¹. Some critically ill patients lack surrogates who might provide informed consent. When available, surrogates may be overwhelmed and desperate, and they may confuse treatment with research thus resulting in inconsistencies between their interests/values and that of the patients. This was illustrated by a recent article in Critical Care Medicine where both patients and surrogate decision makers were presented with hypothetical research scenarios of increasing complexity. The authors noted significant discrepancies between the patients and their surrogate decision makers as the risk of the study increased⁴². Federal guidelines are based on a model of patients providing consent, and few state laws define the role of surrogates.
7. There is no reasonable way to identify prospectively individuals likely to become eligible for participation:
 - a. There are no objective measures that are 100% sensitive and specific in anticipating who will require mechanical ventilation in the intensive care unit. There are several physiologic variables, e.g. $RR > 35$, $SaO_2 < 90\%$, $PaCO_2 > 60$ that, if present, may result in the patient requiring intubation. However, consenting patients based on these variables is neither sensitive nor specific enough to be feasible within the context of the current study. Anticipating who will receive an intervention and who will end-up in extremis in the intensive care unit is equivalent to a coin toss. To prospectively

- consent every patient that is admitted to an intensive care unit can potentially result in the use of considerable resources and costs, particularly for large studies. This is clearly not feasible. There are no indicators with 100% sensitivity and 100% specificity to establish who will require an intervention and who will not or who will become unstable and who will not. The authors feels that unless the patient can be consented prior to the event in a time period deemed feasible and for which the event rate is high, wavier of informed consent is likely the only option for study completion. For example, in a study performed at Mayo Clinic involving silver coated endotracheal tubes, even for non-urgent intubations that could be anticipated, 266 patients were consented but only 180 actually ended up intubated. This means that over 30% of the patients identified as likely to be intubated were never intubated in actuality [unpublished data].
- b. Additionally, analyzing our own database reveals that blanket consent is not feasible. The ICU's that we intend to use for this study had 3,531 unique admissions with only 250 unique intubations in 2012. This is only a 7% intubation rate [unpublished data].
8. Participation in the research holds out the prospect of direct benefit to the subjects:
- a. Critically ill patients requiring emergent intubations are in a life-threatening situation and may benefit from the drug admixture regarding maintenance of mean arterial pressure. As referenced above, clinical trials performed in several settings demonstrate the potential benefits that this drug admixture may have on hemodynamics. These same studies also address the safety of this admixture both from a pharmacokinetic viewpoint and from a patient safety standpoint. The morbidity endpoint of hemodynamic instability, e.g. post-intubation hypotension was chosen rather than the mortality endpoint as critically ill patients who develop post-intubation hypotension of any duration have an associated increased mortality and length of stay. This was demonstrated recently by a retrospective study addressing the incidence of post-intubation hypotension and its possible association with in-hospital mortality. The authors defined post-intubation hypotension as a systolic blood pressure less than 90mmHg occurring within 60 minutes of emergency intubation. Post-intubation hypotension occurred in over 20% of the 465 patients who underwent emergent intubations and was associated with significantly higher in-hospital mortality and longer intensive care length of stay⁴³⁻⁴⁴. The association between post-intubation hypotension and mortality has been confirmed by other groups upon analysis of respective databases⁴⁵. The incidence of post-intubation hypotension varies widely and in certain patient populations (sepsis), it is noted to be as high as 60%⁴⁶. A recent study assessing the incidence of post-intubation hemodynamic instability defined as systolic blood pressure less than 90mmHg, a decrease in systolic blood pressure of greater or equal to 20%, a decrease in mean arterial pressure to less than or equal to 65mmHg, or the initiation of any vasopressor within the first 30 minutes following intubation found an incidence of 44%. These authors demonstrated an increased mortality and hospital length of stay in those patients who developed post-intubation hemodynamic instability⁴⁷.
9. The clinical investigation could not practically be carried out without the wavier:
- a. It is neither feasible nor practical to obtain consent from all critical care patients admitted to the respective intensive care units at Mayo Clinic due to the infrequent nature of the intervention, e.g. endotracheal intubation. Only a small fraction of patients admitted to the critical care units at Mayo Clinic will become ill enough to receive the above intervention and therefore enrollment would take too long to conduct the study in a reasonable amount of time. Please see above regarding unpublished data.

Intubation Period: Patients will receive standard intensive care unit monitoring consisting of electrocardiogram analysis, pulse oximetry and a noninvasive blood pressure cuff. The presence of invasive monitors such as an arterial line will be allowed. Hemodynamic measurements will be based off the noninvasive devices and/or invasive arterial line measurements if the noninvasive measurements are not available. Once the decision to intubate the patient is made by the clinical team, both the unit Registered Respiratory Therapist (RRT) and the assigned bedside nurse will be informed as per usual practice. The unit RRT will notify the lead RRT and core study staff to immediately be present at the patient's bedside. The lead RRT or core study staff will serve as the time/record keeper and will collect the necessary information prospectively. The core study staff will review eligibility and attempt to obtain consent, during business hours. The unit RRT will reset the time intervals on the electronic medical record within the patient's ICU room to record every one minute until 15 minutes after successful intubation and then switch to 5 minute intervals for the remaining 45 minutes post intubation for a total duration of 60 minutes post-intubation. They will then assist with the intubation per usual practice. Hemodynamics closest to study drug administration will be recorded prior to induction as a baseline. To an extent, the anesthetic is to be controlled. At induction, the trial drug will be administered over 60 seconds along with fentanyl at 50mcg. Nursing will document the amount of drug administered in the electronic medication record. The dose charted will be verified with the amount recorded by the lead RRT or core study staff for accurate study drug reconciliation. Neuromuscular blockade as deemed necessary by the critical care provider will be allowed. Midazolam as deemed necessary by the critical care provider will be allowed. Intubation times will be recorded by the lead RRT or core study staff. The time from study drug administration to intubation will not be standardized. After intubation, sedation is then to be maintained with the choice decided by the critical care provider. Additional narcotics will be allowed as necessary throughout the study period. If necessary, anti-cholinergics, vasoactive and steroid medications are to be allowed as well. Hemodynamics (mean arterial pressure, systolic blood pressure, diastolic blood pressure and heart rate) will be recorded every minute until 15 minutes after successful intubation and then every 5 minutes up to 60 minutes post-intubation. Time zero would be defined as time of study drug administration. Emergence from anesthesia will not be controlled by the study protocol.

C.9. Study Measures/Assessments

Hemodynamic Assessment: Noninvasive blood pressure measurements and/or arterial line measurements prior to study drug administration will be obtained and up to one hour after successful intubation. For the first 15 minutes post-administration of study drug measurements will be taken every one minute. Following this interval, the measurements will then be switched to intervals of 5 minutes until the time period of one hour has elapsed since successful intubation. Data will be obtained from the chart from the period of 1 hour prior to intubation and 1 hour after intubation.

Clinical Assessment: General characteristics of the patient including demographics, hemodynamics (average of values 60 minutes prior to intubation), cardiovascular medications, and APACHE 3 score for the time period of 24 hours prior to study drug administration will be obtained. Final diagnosis is to be recorded. Interventions including transfusions, total fluid volume, urine output, total amount of analgesic/sedative medications utilized, vasopressor/steroid administration, intensive care unit-confusion assessment method scores and mechanical ventilation parameters will be recorded during the study period of 24 hours pre and post-drug administration.

Quality Control Measures: The quality of randomization will be accounted for by the study coordinator. They will ensure an accurate record of those participants who received a particular intervention. We will utilize Redcap data management system. A core set of study staff will be trained in the protocol and for study related tasks such as eligibility assessment and obtaining consent. Furthermore, the core study staff will be contacted bi-monthly to review

study progress and concerns voiced to them from the clinical care team. The study coordinators will also schedule routine meetings with the PI to review adverse events and protocol deviations. . The decision to conduct an interim analysis will be governed by the DSMB and the DSMB charter. Regarding ketamine, emergence phenomenon is a concern and this will be assessed by recording intensive care unit-confusion assessment method scores in the intensive care unit during the follow-up period. To ensure proper doses of medications given, tables will be provided to the bedside nurses within and outside the randomization envelopes with the correct dose of both drugs to be given according to the weight of the patient. The weight closest to the intubation will be used to guide drug dosing, unless health care provider requests a prior weight to be used, then the reason for using other weight will be documented on the recorder form.. The unit nursing team will be provided with education. Please see separate document regarding Data Safety Monitoring Board (DSMB) charter.

C.10. Data Analysis

For all analyses, distributional assumptions will be assessed with data transformations or non-parametric methods used as appropriate. For the primary analysis, the change in mean arterial pressure from baseline to 5 minutes post induction will be compared between groups using analysis of covariance with shock state, dose included as a covariate. Secondary analyses will be performed to compare mean arterial pressure change from baseline at 10 and 15 minutes as well as the average mean arterial pressure area under the curve over the first 15 minutes expressed as a change from baseline. Secondary analyses will also be performed to assess whether treatment differences are dependent on stratification factors. Additional endpoints (28 day/in hospital mortality, mechanical ventilation free days at in hospital/day 28, vasoactive medication use, transfusions, fluid loading ($\geq 30\text{cc/kg}$ and intensive care unit free days at in hospital/day 28) will be summarized separately for each group and compared between groups using appropriate 2-sample methods (e.g., Fisher's exact test or ANOVA). Additionally, we are particularly interested in the subgroup of patients on vasoactive medications and those who have received at least 30cc/kg of fluid within three hours prior to intubation. Therefore, subgroup analyses will be performed for these two subgroups. In all cases, two-tailed tests will be used with p-values of 0.05 or less considered statistically significant.

- **Primary Endpoint (Mean Arterial Pressure Over 5 Minutes):** The primary outcome of interest is change in mean arterial pressure from baseline over the first 5 minutes following induction. Data will be recorded at baseline and every minute thereafter. The primary endpoint will focus on the change in mean arterial pressure at 5 minutes post-induction.
- **Secondary Endpoint #1 (Mortality Difference):** We will analyze differences in 28-day/in-hospital mortality between the two groups. This will be stated as alive or dead at the 28-day mark or hospital discharge, whichever comes first and obtained through the medical charts for comparison between the two groups using appropriate 2-sample methods.
- **Secondary Endpoint #2 (Vasoactive Medication Use):** We will analyze the difference in the use of vasoactive medications between the two groups. This will be obtained through the medical chart and compared between the two groups using the appropriate 2-sample methods.
- **Additional analyses:** Additional secondary endpoints will include mechanical ventilation free days at day 28, or hospital discharge, whichever comes first, transfusions, fluid loading ($\geq 30\text{cc/kg}$) and intensive care unit free days at day 28, or hospital discharge, whichever comes first.
- **Adrenal Assessment:** As part of the earlier protocol Version 5, a cosyntropin stimulation test was performed by administering 250 mcg cosyntropin at approximately the 4 and 24 hours. Serum cortisol levels were drawn at approximately 1 hour before and 1 hour after the cosyntropin dose. We would now like to analyze the results in the subset of 39 patients which provided consent and had this testing performed. The test will be considered normal if the pre-cosyntropin cortisol is greater than 10 mcg/dL or if the post-cosyntropin cortisol rises by more than 9 mcg/dL [48].

C.11. Sample Size Considerations

The sample-size for the current study was based on the assumption that the standard deviation for the change in mean arterial pressure from baseline to 5 minutes post induction is approximately 10 mmHg, and that the mean difference between groups needs to be at least 5 mmHg in order to be considered clinically relevant. Based on these assumptions, we have determined that a sample-size of N=64 per group will provide statistical power (two-tailed, $\alpha=0.05$) of 80% to detect a clinically relevant difference (i.e., difference of 5 mmHg) between groups. We designed the study to have adequate statistical power to detect a 5 mmHg difference between groups using a two-sided test. In addition to performing the hypothesis test we will also calculate a 95% confidence interval for the difference between groups. 128 is the effective sample-size (i.e., the number of subjects we need who have data for the primary outcome). Increasing the sample-size to allow for 20% subject attrition (drop-out) will be undertaken given the critical nature in which the study will be conducted. Increasing the sample-size to 160 would allow for 20% drop-out (i.e. 80% of 160 = 128). Therefore, we will enroll a total of 160 research participants.

D. Protection of Human Subjects

D.1. Consenting

Research enrollment in the critical care environment, particularly, due to the nature of this study, is likely to include surrogate consent in situations where a surrogate is available and the research subject is unable to provide consent because of the degree of their critical illness. To ensure that patients are appropriately protected, all patients for which surrogate consent is obtained will have the opportunity to provide continuing consent for participation in the study. In cases where continuing consent cannot be obtained, for instance, continued incapacitation or death, such reasons for not obtaining continuing consent will be documented in the patients study file by the study coordinators with times documented as well. In addition, because of the emergency nature of this study, a community consultation and consent plan have been filed with the FDA. Please see the Community Consultation and Consent Plan Document for further information.

All patients enrolled in the trial will have an enrollment note placed in the chart within 72 hours to confirm they were enrolled. All patients will be notified within 90 days of trial involvement. After the first contact during the 90 day period, two additional phone calls will be made 2 weeks apart. If on the final attempt, there is still no contact with the patient or patient's legally authorized representative, a certified letter will be sent.

D.2. Data Protection

To ensure the protection of patient data, all study data is stored on an encrypted, restricted access server maintained behind Mayo Clinic's firewall. Only study staff will have access to this information. In the event that paper documentation exists for research subjects, their research folders will be maintained in a locked cabinet in a building with restricted access. Only study staff will have access to the files. After data analysis, study records will be stored for a duration according to regulation and subsequently destroyed.

D.3. Assessment of Safety Adverse Event Definitions

Adverse Event: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Life-threatening Adverse Event or Life-threatening Suspected Adverse Reaction: An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious Adverse Event or Serious Adverse Reaction: An adverse event is defined "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of

existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Suspected Adverse Reaction: Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of investigational new drug (IND) safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unexpected Adverse Event or Unexpected Suspected Adverse Reaction: An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the drug package insert or is not listed at the specificity or severity that has been observed.

Patients that are critically ill and requiring intubation with respiratory support sustain multiple adverse events as a result of their medical condition. Therefore, only adverse events that have medical importance and/or may have a causal relationship to etomidate, ketamine or propofol will be reported.

D.4. IND Safety Reports

The study team will notify the FDA in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies as "Serious and Unexpected Suspected Adverse Reaction". Results of other studies suggesting significant risk to humans exposed to drugs used in this trial, any trials conducted in animals or in-vitro testing that suggests significant risk to humans exposed to the drug, or a clinically significant increased rate of occurrence of serious suspected adverse reactions will be reported. In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information. Adverse events possibly related to etomidate or ketamine / propofol administration include but not limited to tachy/bradycardia, hypo/hypertension, nausea/vomiting, hallucinations, disorientation, anxiety, myoclonus, seizures, anaphylaxis, arrhythmias, fatal anaphylaxis and anaphylactoid reactions, adrenal suppression and pain upon injection.

D.5. Timing of Adverse Event Assessment

Adverse events (AEs) will be assessed for 72 hours with specific attention to 18 hours after enrollment. In the event that a patient is discharged from the hospital before the 72 hour period is up, we will contact the patient by phone. AEs will be reported to the Mayo Clinic IRB in a manner consistent with the site's institutional policy.

D.6. Annual AE and SAE Summaries

The study team will ensure that annual reports are submitted to the IRB and will contain (a) the number of adverse events and an explanation of how each event was handled, (b) the number of complaints and how each complaint was handled, (c) the number of withdrawals of study participants and an explanation for each withdrawal, and (d) the number of protocol violations and how each was handled. Summaries of SAEs will be provided to the Data Safety Monitoring Board (DSMB) at intervals determined by the DSMB, and DSMB reports and communications will be passed onto the Mayo Clinic Institutional Review Board.

D.7. Safety Oversight

Safety oversight will be under the direction of a DSMB whose members will be independent from the study operations, will regularly review safety data consisting of AEs and protocol deviations throughout the study duration. Full details of the composition and the operation of the DSMB and how the safety analyses are to be performed will be detailed in a separate DSMB written charter. Enrollment may not begin, even with IRB and FDA approval, until the DSMB has been notified of the current protocol.

D.8. Assessment of Toxicity

The study team will adopt the grading system toxicity as published by the FDA in September of 2007 in the guidance entitled, "Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials." This severity scale will apply to any laboratory values or clinical abnormalities that fall outside of the institutions normal value range. The study investigator will sign off on the level of toxicity for any abnormal lab value or clinical symptom/sign.

D.9. Assessment of Causality

The study team will adopt the WHO-UMC system for standardized case causality assessment, highlighted in Table 1.

Table 1:

Causality term	Assessment criteria*
Certain	<ul style="list-style-type: none"> • Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/ Likely	<ul style="list-style-type: none"> • Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	<ul style="list-style-type: none"> • Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	<ul style="list-style-type: none"> • Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	<ul style="list-style-type: none"> • Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	<ul style="list-style-type: none"> • Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

*All points should be reasonably complied with

D.10. Study Stopping Rules

D.10.1. Futility

In order to ensure adequate statistical power for the primary analysis and not jeopardize the analyses of secondary outcomes, no interim analyses or early-stopping rules are included.

D.10.2. Safety

Judgment concerning the continuation or termination of the study will only be based on recommendations from the DSMB. The DSMB will play a valuable role in advising the study leadership on the relevance of advances in the diagnosis and treatment of patients. A number of therapeutic or diagnostic testing advances may possibly occur during the course of the trial. The DSMB will need to help put these advances in proper perspective. If protocol modifications are warranted, close consultation among the DSMB, the FDA, and the study Primary Investigator will be required. The principal investigator has the power to stop the study at any time.

D.11. Immediate Study Subject Stopping Rules

The study will not delay intubation in patients. Clinicians will proceed per standard of care. In the event the study drug is not available by the time of intubation, the procedure will proceed in the usual fashion per clinician's preference. The study will effectively be stopped in such cases.

In addition, if patients exhibit hemodynamic instability within 5 minutes prior to study drug administration, the study will be stopped. The procedure will proceed in the usual fashion per clinicians preference. Hemodynamic instability will be defined as:

- 1) Heart rate greater than 160 or less than 50;
- 2) Systolic blood pressure greater than 180 or less than 70;
- 3) Diastolic blood pressure greater than 120 or less than 30.

E.1. Public Disclosure

The investigator will notify the community of the clinical trial results. The Center for Clinical and Translational Science (CCaTS) will assist with the public disclosure plan. A public podcast will be held to share the clinical trial protocol information, including inclusion population and their characteristics, primary and secondary endpoints, adverse events and conclusions. The podcast will be coordinated by CCaTS community engagement specialists.

Appendix A. Resource Summary

ST. MARYS HOSPITAL and ROCHESTER METHODIST HOSPITAL

Mayo Clinic Hospitals: Mayo Clinic is the nation's largest group practice encompassing world renowned clinical and surgical expertise with extensive research and educational activities. Mayo physicians exclusively staff two large hospitals. Saint Marys (1,157 licensed beds) and Rochester Methodist (794 beds), which are part of Mayo Clinic. The organization attends nearly half a million patients each year from all regions of the United States and many countries abroad, although the majority are from within a 500-mile radius of Rochester. The 213 ICU beds and 24/7 intensivist staffing provide unrestricted access to ICU services and life support interventions to the Olmsted county community.

The Division of Biomedical Statistics and Informatics (BSI) in the Department of Health Sciences Research was formed in late 2008 by merging the Division of Biostatistics with the Division of Biomedical Informatics to facilitate the linkage of traditional biostatistics and modern computational techniques. This division presently comprises more than 200 members, including faculty, programmers, contracting personnel, and support personnel. BSI provides integrated collaborative research support in both biostatistics and biomedical informatics. This model of collaboration was introduced by Joseph Berkson (known for the Berkson bias) in 1932. BSI has also supported the integrated medical record at Mayo since 1907 and has organized the retrieval indices that have made Mayo an unparalleled resource for clinical research.

BIostatISTICS SUPPORT

Biostatistics expertise is provided by 25 PhD statisticians and 55 statisticians with master's degrees, whose activities are facilitated by 75 statisticians with bachelor's degrees (statistical programmer analysts), and 20 clerical personnel. In addition to general consulting on over 2,000 ongoing investigations, the statistical group provides core statistical support for a number of program projects. The biomedical informatics activities within the division have two principal missions: (1) the indexing and organization of data generated by the clinical practice for search and retrieval in support of research and education; and (2) a program of basic research on clinical concept representation, information indexing, and database retrieval. This group is represented by 11 PhD research investigators, 8 MS or PhD informaticists, 23 analyst programmers, and 24 additional support staff. During the past 3 years, the division has established a close working relationship with IBM Life Sciences Division to design, prototype, and deploy a comprehensive information archive of basic science data, genomic data, clinical data, natural language processed documents, and metadata. The division also maintains an active statistical research effort, especially in the areas of epidemiologic modeling, survival analysis, and statistical genetics and in the design, early stopping, and analysis of clinical trials. Recently, four sections were created in BSI to ensure scalability of resources and facilitate mentoring. While sections have been created, careful attention has been given to minimize the likelihood of forming silos within and among sections. In that spirit, this application will enable synergy across the full resources of BSI rather than in only one section. BSI is one of the key institutional units integrated into the CTSA. BSI is the academic home for the CTSA BERD program and the Biomedical Informatics CTSA component.

MINORITY RECRUITMENT RESOURCES

The Office for Diversity in Clinical Research (ODCR) provides Mayo Clinic researchers with information and advice on protocol design, identification of target populations, and development of minority recruitment strategies, and assists in the recruitment of participants to research protocols throughout the community and nationwide. Its mission is to: increase and deepen community relationships with minority populations through outreach; act as a liaison between the community and the research teams; honor cultural ways of health and healing in education, patient care, and research; communicate medical and scientific concepts with culturally relative tools; and, within Mayo's region, identify and attempt to change the social and cultural factors that inhibit access to appropriate care and participation in clinical care and research opportunities. Mayo's Native American Programs at the Cancer Center provide links to local Native American communities; Mayo has established a formal understanding with the Indian Health Service to facilitate research on cancer and related health burdens. These two offices will help facilitate minority recruitment and representation in our studies.

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